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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/532,879

04/25/2006

Bent Karsten Jakobsen

006090.00017

9328

22907 7590 10/08/2008

BANNER & WITCOFF, LTD.

1100 13th STREET, N.W.

SUITE 1200

WASHINGTON, DC 20005-4051

EXAMINER

WESSENDORF, TERESA D

ART UNIT

PAPER NUMBER

1639

MAIL DATE

DELIVERY MODE

10/08/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



**DETAILED ACTION**

***Election/Restrictions***

Applicants assert that claim 1 does not specify whether the bond is the native bond or an introduced bond. Therefore claim 1 encompasses displayed TCRs which are either natural (only applicable of course to heterodimeric TCRs) or "mutated" or "modified" by the introduction of an artificial interchain bond (applicable to both dimeric and single chain TCRs). Hence claims 88 and 89, which specify non-natural, introduced interchain bonds, are properly dependent on claim 1. Applicants note that withdrawal of claims 88 and 89 is inconsistent with the examination of claims 86 and 87, which also relate to mutated TCRs.

In reply, as stated by applicants above claim 1 is a natural heterodimeric TCRs as there is nothing in claim 1 that recites for a mutated form especially as specifically recited in claims 88 and 89. Thus, while claim 1 can read on modified TCR however, modification can be done in the different residues not necessarily in the selected residues and with particular amino acid residues as recited in claims 88 and 89. Accordingly, these claims have been properly withdrawn from consideration as encompassing different scope from the original claim 1.

***Status of the Claims***

Claims 1, 6, 55-59 and 86-89 are pending in the instant application.

Claims 55-59 and 88-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. [Note that claims 88-89 are drawn to a modified or mutant form of a TCR bound phage. However, claim 1 does not recite a mutant or a modified form of said TCR. Accordingly, these claims to a mutant (i.e., by substitution) have been withdrawn from consideration.]

Claims 1, 6 and 86-87 are under examination.

***Withdrawn Rejections***

In view of the amendments to the claims and applicants' arguments, the 35 USC 101, 35 USC 112, first and second paragraphs and 102 over Nissim and Weidanz (I and II) rejections are withdrawn.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to describe the composition of the polypeptide comprising the first and second polypeptides. The specification at page 17, lines 8-20 only mentions in general terms as what is also claimed i.e., first and second polypeptides. A skilled artisan cannot readily ascertain whether the first and second polypeptides flanking the TCR, if this is the intent of the claimed scope are the same or different or if the entire first and second polypeptides consist only of dimeric TCR. The claimed first and second polypeptides would encompass numerous residues individually or in combinations, not to mention the length, encompassed by said huge first and second polypeptides.

***Claim Rejections - 35 USC § 112***

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "first and second" polypeptides in claim 1 are relative terms which render the claim indefinite. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There are no differentiating features of what constitutes first and second polypeptides or whether the first and second polypeptides are the TCR dimers itself. There are no clarifying features of said first and second polypeptides, except in the passing remarks at page 17 of said terms in the disclosure. Explanation/clarification is requested.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

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the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz [(J. Immunol. Methods) (I) or (WO 99/18129) (II).] (as evidenced by Reiter et al (Immunity)).

Weidanz (I) discloses at e.g., page 59, abstract, a bacteriophage display on its surface a dimeric T cell receptor comprising an interchain disulfide bond linking residues of constant domain sequences. See also page 60, col. 1 and col. 2 and page 73, col. 1.

Claim 6 linking of TCR at the C-terminus to the N-end of phage is disclosed at page 73, col. 2.

Claims 86 and 87 which recite a disulfide bond would be inherent to the TCR dimer which is formed by the disulfide bonds between the alpha and beta TCR region.

Weidanz (II), throughout the patent, basically discloses the same dimer TCR as disclosed at e.g., the abstract.

### ***Response to Arguments***

Applicants assert that Weidanz I does not disclose all the features of the phage particle recited in claim 1. First, all the phage-displayed TCRs disclosed in Weidanz I are single-chain TCRs containing at most three domains (Va-linker-Vl3Cl3). See

Figures 1a and 1b on page 66, which illustrate the two and three domain single-chain TCR constructs discussed in this paper. See also the Abstract on page 59, especially lines 4-5.3 Section 2.3 on page 61, "Construction of scTCR fusions," explains that "[t]he Va and V13C13 domains were linked together by a (G48)<sub>4</sub> peptide linker." The final paragraph of that section makes it clear that the phage-displayed anti-p53 TCR construct contained the first seven N-terminus amino acids of the Ca domain (APEPNQI) fused to the C-terminus of the Va domain in the three domain scTCR construct utilized. Moreover, the phage-displayed single-chain TCR constructs in Weidanz I disclosed do not contain an interchain disulfide bond within the TCR portion thereof of any description. See page 65, section 3.1, final paragraph, which explains that the phage-displayed scTCR constructs disclosed were "truncated at the amino acid just prior to the final cysteine." This truncation removes the cysteine residue from the TCR 13 chain that is involved in forming the interchain disulfide bond in native TCRs. On page 61, section 2.3, right column Weidanz I explains that the phage-displayed scTCR constructs disclosed either contained no part of the Ca domain, or only the seven N-terminus amino acids of the Ca domain (APEPNQI) fused to the C-terminus of the Va domain in the three domain scTCr construct utilized. These seven N-

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terminus amino acids at the amino acid present in this portion of the wild-type CGt domain and are not capable of forming a disulfide interchain bond with the CI3 constant domain. The cysteine residue from the TCR Gt chain that is involved in forming the interchain disulfide bond in native TCRs occurs near the C-terminus of the extracellular portion of the CGt domain and is therefore not present in any of the disclosed phage-displayed scTCR constructs. The examiner asserts that claims 86 and 87, which recite a disulfide bond, would be inherent to the TCR dimer which is formed by the disulfide bonds between alpha and beta TCR chains. However, claims 86 and 87 additionally specify that the recited interchain disulfide bonds must not correspond to the interchain disulfide bonds found in native TCRs.

### ***Response to Arguments***

In reply, the suggested teachings of Weidanz I in the footnote, as quoted by applicants at page 12 of the instant REMARKS suffice the finding of obviousness.

Applicants state:

Weidanz I mentions a (hetero)dimeric TCR construct (page 60, first column, first paragraph); however, this comment is in relation to the native TCR, not the phage-displayed TCR construct generated from it.

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It would be within the ordinary skill in the art to fuse said heterodimeric TCR to a phage display since as applicants stated above this has been done for the single chain TCR. Whether said heterodimer is synthetic or a natural one is immaterial, inasmuch as the product is known. As applicants stated above claim 1 reads on natural or non-natural TCR dimer. It would be within one having ordinary skill in the art to determine the disulfide bond linkage, which as applicants stated above, is native to a TCR(or antibodies). It is well known in the art that TCR(or antibodies) are naturally linked by disulfide via the non-reactive constant regions. This is evident from the teachings of Reiter at e.g., page 281, Summary heading:

Disulfide-stabilized Fvs (dsFv) are recombinant Fv fragments of antibodies in which the inherently unstable V<sub>H</sub>-V<sub>L</sub> **heterodimer is stabilized by an interchain disulfide bond engineered between structurally conserved framework positions**. We now design and produce a disulfide-stabilized Fv of sT cell receptor. It is composed of V<sub>α</sub> and V<sub>β</sub> variable domains of the 2B4 TCR stabilized by a disulfide bond between framework residues of the TCR Fv at a sites corresponding to that used for disulfide stabilization of antibody Fvs. For ease of production and detection, the TCR dsFv was fused to a truncated form of Pseudomonas exotoxin (PE38). The TCR(dsFv) retains its native conformation and is much more stable than sTCR scFv. Moreover, it is functional in biological assays. Because successful disulfide stabilization of the TCR Fv by the positions used for antibody Fv stabilization would not occur unless the mutated residues in TCR Fv are at positions closely similar to those in antibody Fvs, most likely within less than 1.5 Å, these results provide very strong experimental evidence for the structural similarity between immunoglobulin and TCR antigen- binding variable domains. (Emphasis added).

Applicants assert that Weidanz II also lacks disclosure of a construct as claimed in the present application in this document (i.e. a phage particle displaying on its surface a single chain or dimeric T cell receptor comprising an interchain disulfide bond linking residues of constant domain sequences). The two and three domain scTCR constructs disclosed in Weidanz I are also disclosed in Weidanz II, which contains the following disclosure (on page 15, lines 15-29; (emphasis added) relating to the length of the TCR constant domain sequence that may be included in such three domain TCR constructs: The V-Gt chain of the sc-TCR molecule can further include a C-13 chain or fragment thereof fused to the C-terminus of the V-J3 chain. Further, the V-Gt chain can include a C-Gt chain or fragment thereof fused to the C terminus of the V-Gt chain and the N- terminus of the peptide linker sequence. Generally, in those fusion proteins including a C $\alpha$  chain fragment, the fragment will have a length of approximately 50 to 126 amino acids and will usually not include the last cysteine residue at position 127. For those fusion proteins comprising a C-a chain, the length can vary between approximately 1 to 90 amino acids (i.e., the C $\alpha$  chain up to but not including the final cysteine). For example, in one embodiment, the fusion protein includes a C-a chain fragment

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between about 1 to 72 amino acids starting from amino acid 1 to 72. In another embodiment, the C- $\alpha$  chain fragment is between about 1 to 22 amino acids starting from the first amino acid to 22 (leucine). The C $\alpha$  chain fragment typically does not include any cysteine residues except the C-90 variant which includes two cys residues. The absence of cysteines according to the above directions of course excludes the possibility of an interchain bond between residues in the constant regions. Moreover, in all three Weidanz II fragments, the C $\alpha$  chain fragment ended at a cysteine residue. This "final" cysteine was changed to a serine residue but no internal cysteines were mutated. Final construct pKC73 has 22 amino acids of the C $\alpha$  chain, pKC74 has 72 amino acids, and pKC75 has 90 amino acids (i.e., the entire C $\alpha$  chain). See Figure 9A, which schematically represents the pKC73, pKC74 and pKC75 DNA vector inserts. None of these inserts contains a disulfide interchain bond in their constant regions.

In response, applicants' arguments as to the mutations of the sequence are not commensurate in scope with the claimed invention, at least claim 1. Nonetheless, the disclosure of Weidanz, or at least suggestion, that the native disulfide bond can be mutated does not detract from its teachings that such modification can be done on the natively occurring disulfide bond.

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Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Boulter et al (Protein Eng'g) in view of Schumacher, (EP 1,118,661).

Boulter discloses at e.g., page 707, col. 2:

...[D]esign of a generic method for producing soluble human TCRs, stabilized by a non-native disulphide bond between the extracellular and constant domains. Molecular modeling was used to determine the optimal site for the disulphide bond, and three recombinant soluble TCRs were produced in Escherichia coli and refolded with high efficiency. The disulphide-linked TCRs (dsTCRs) were highly stable and displayed authentic binding activity.....the design of the dsTCRs makes them highly amenable to crystallization and ....the preliminary crystallization of one dsTCR along with crystallographic analysis confirming the inter-chain disulphide bond position. These dsTCRs are likely to be amenable for in vivo therapeutic applications, and candidates are currently being developed for clinical applications....

Boulter does not disclose the dsTCRs fused to a phage display surface. However, Schumacher discloses at e.g., paragraph:

[0003] For the in vitro isolation and generation of monoclonal antibodies, antibody phage display has proven to be a useful technology to replace hybridoma technology and animal immunization. Recently, the expression of single-chain TCRs by filamentous phages has likewise been achieved and this approach may conceivably be used to produce phage display libraries for TCR selection purposes. However, the ability of T cell membrane-associated TCRs to discriminate between closely related ligands appears to be directly related to the property of TCRs to cluster upon encounter of their cognate ligands 5,6, and it may prove difficult to copy this process on phage...

Accordingly, it would have been obvious to one having ordinary skill in the art to fuse the TCRs of Boulter to a phage display. Schumaker teaches that phage has been used to display TCR. One would have been motivated to fuse it to said phage for the advantage in the use of said vectors i.e., the possibility to directly test the function of selected TCRs. One would have a reasonable expectation of success since phage display has been known to successfully replace the recombinant hybridoma technology or immunization. Phage has also been known to successfully fuse the immune system, antibodies.

The Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." . . . [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." .. KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007), 2141 to 2145.

No claim is allowed.

**Conclusion**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**This application contains claim55-59 and 88-89 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639

<div>Application Number</div> <div></div>	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/532,879	JAKOBSEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	